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► **To cite this version:**

Natacha Go, Caroline C. Bidot, Catherine C. Belloc, Suzanne Touzeau. Modelling of immune response to a respiratory virus targeting pulmonary macrophages : exploration of the host susceptibility and viral virulence.. SBIP 2013: Systems Biology Approach to Infectious Processes, May 2013, Lyon, France. 16 diapos. <hal-01000672>

HAL Id: hal-01000672

<https://hal.science/hal-01000672v1>

Submitted on 6 Jun 2020

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HAL Authorization

SBIP 2013 — *Systems Biology Approach to Infectious Processes.*

Lyon, May 13-15th 2013

MODELLING OF IMMUNE RESPONSE TO A RESPIRATORY VIRUS TARGETING PULMONARY MACROPHAGES: EXPLORATION OF THE SUSCEPTIBILITY AND VIRULENCE

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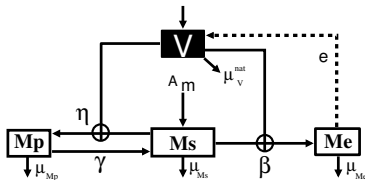
INTRODUCTION

- **Background:** control of respiratory infections
- **Needs:** better understanding of immune dynamics
- **Focus:** virus targeting pulmonary macrophages
 - ★ phagocytosing vs infected status
 - ★ alteration of the immune dynamics
- **Hypothesis:** macrophage – virus interactions are determining for the infection outcome.
- **Application:** PRRSV = porcine virus targetting pulomary macrophages

⇒ **MODELLING APPROACH** to explore the immune response to PRRSV and its variability

STEPS

Basic model



Model development

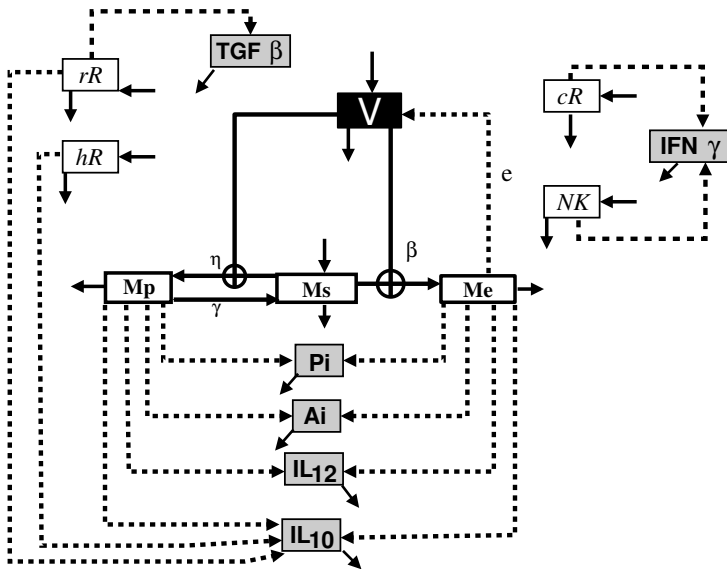
- Cytokine syntheses and regulations
- Adaptive response

⇒ Complex model with 18 state variables and 300 parameters

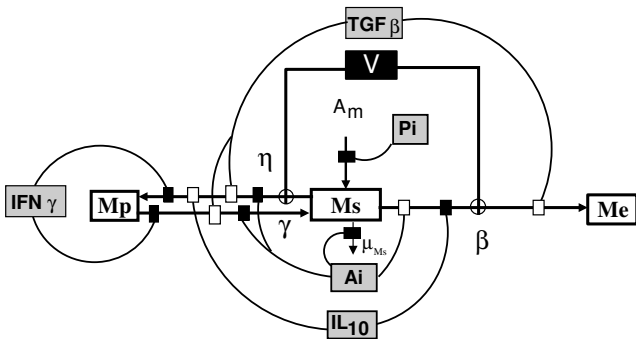
Limits: lack of data → model calibration very difficult

Model simplifications

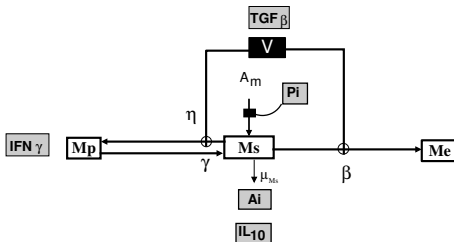
CONCEPTUAL MODEL



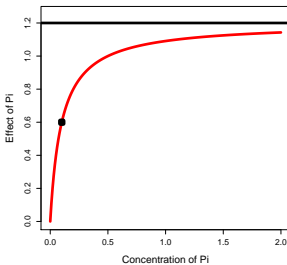
MODEL FORMALISATION



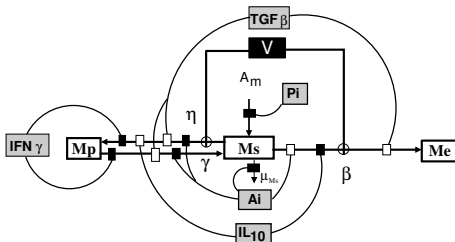
MODEL FORMALISATION



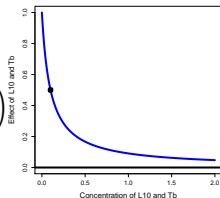
$$\dot{M}_S = A_m \left(1 + \frac{v_m P_i}{k_m + P_i} \right)$$



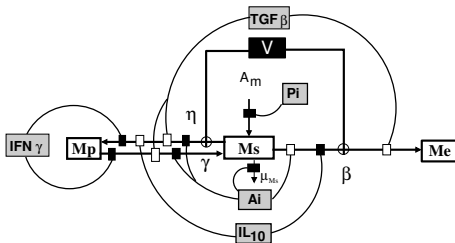
MODEL FORMALISATION



$$\dot{M}_S = A_m \left(1 + \frac{v_m P_i}{k_m + P_i} \right) - \eta M_S V \frac{k_m}{k_m + L_{10} + T_\beta} \left(1 + \frac{v_m (A_i + I_\gamma)}{k_m + A_i + I_\gamma} \right)$$



MODEL FORMALISATION



$$\begin{aligned} \dot{M}_s = & A_m \left(1 + \frac{v_m P_i}{k_m + P_i} \right) \\ & - \eta M_s V \frac{k_m}{k_m + L_{10} + T_\beta} \left(1 + \frac{v_m (A_i + I_\gamma)}{k_m + A_i + I_\gamma} \right) \\ & + \gamma M_p \frac{k_m}{k_m + L_{10}} \left(1 + \frac{v_m (A_i + I_\gamma)}{k_m + A_i + I_\gamma} \right) \\ & - \beta M_s V \frac{k_m}{k_m + A_i + I_\gamma + T_\beta} \left(1 + \frac{v_m L_{10}}{k_m + L_{10}} \right) \\ & - M_s \left(\mu_M^{\text{nat}} + \mu_M^{\text{inf}} \frac{A_i}{k_m + A_i} \right) \end{aligned}$$

Model

- Deterministic mathematical model of 14 ODE and 30 parameters
- Highly complex and non-linear

Data

- **Experimental studies on PRRSV:**

- ★ Viral dynamic in the blood and lung
- ★ Immune dynamic in the lung: insufficient data

⇒ Calibration on viral dynamic output, consideration of the variability and uncertainty.

- **Modelling studies**

- ★ 1 conceptual model of PRRSV infection
- ★ Many models of Influenza and Tuberculosis infection

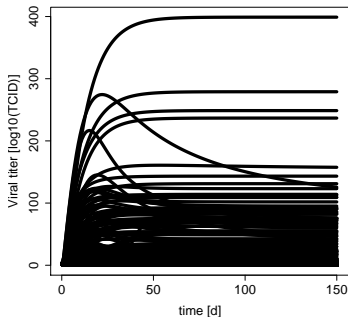
⇒ Setting of large variation range of parameters which need to be refine

METHOD

– Exploration of the large range

- ★ Definition of a **fractional factorial design** (PLANOR library of R)
 - 4096 parameter value combinations
- ★ Model simulations → many viral dynamics

A unique inoculation V_0 at T_0



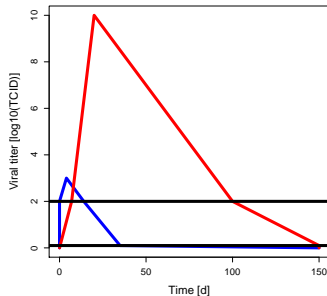
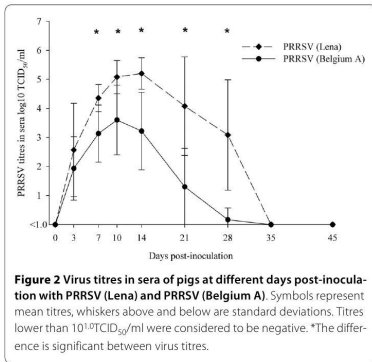
METHOD

- Exploration of the large range
- Selection of parameter values

Inventory of published data



Synthesis and summary in 5 aggregated variables



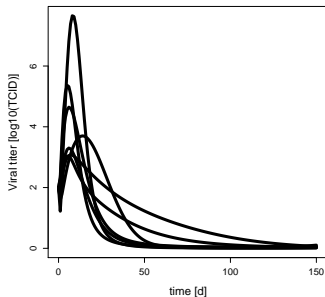
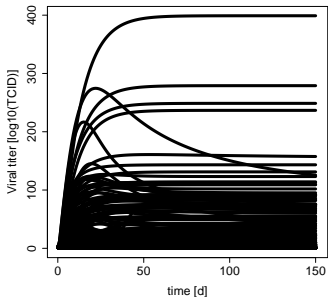
Karniychuk *et al.* BMC Veterinary Research

2010, 6:30

Peak beginning, Peak date, Viral titer at peak,
Peak ending, Resolution Date

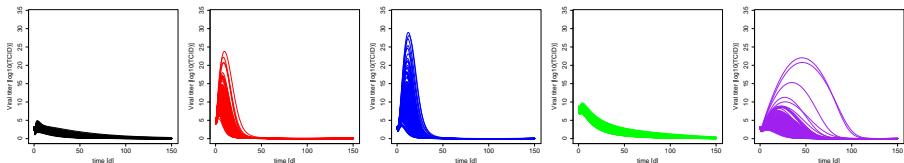
METHOD

- **Exploration of the large range**
- **Selection of parameter values**
 - ★ Definition of the variation range for each criterion representing the variability & uncertainties
 - ★ Identification of the parameter combinations resulting in simulations which comply each criterion



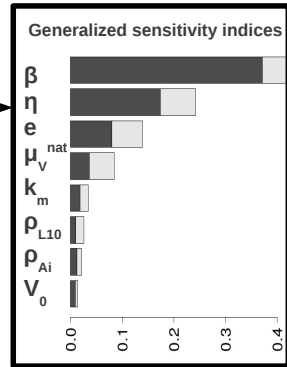
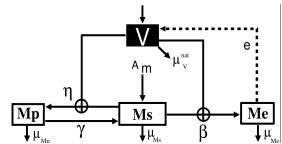
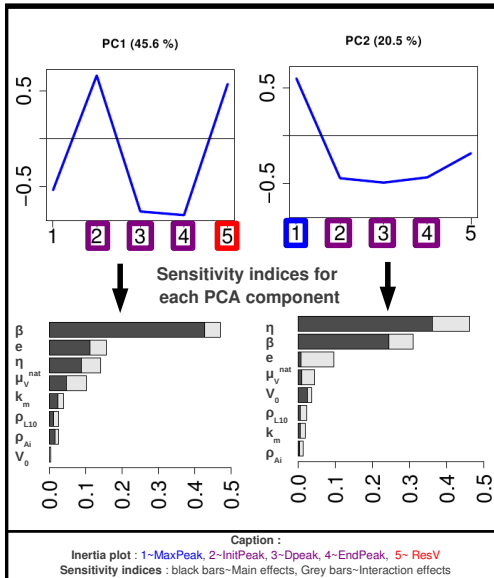
METHOD

- **Exploration of the large value range**
- **Selection of parameter values**
- **Model robustness** (first approach)
 - ★ Selection of 5 combinations corresponding to contrasted dynamics
 - ★ Definition of 5 designs with a 10% variation
 - ★ Model simulations ($5 \times 2187 = 10935$)

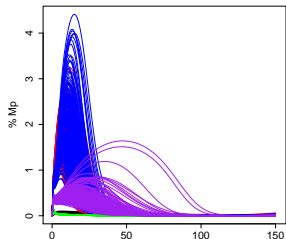
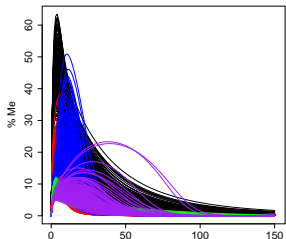
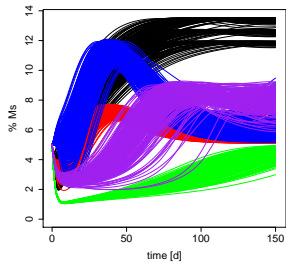
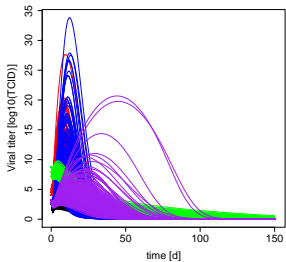


- ★ Multivariate sensitivity analysis of the parameter influence on criteria variance

SENSITIVITY ANALYSIS



IMMUNE DYNAMICS



CONCLUSION

Model

- Original model centred on the macrophage – virus interactions
- Simplified representation able to reproduce realistic viral dynamic
- Framework to explore the innate mechanisms for respiratory infections

Calibration

- Method allowing to calibrate the model despite the lack of data
- Consideration of the uncertainties and variability
- **Improvements:** Better exploration of the parameter space & consideration of the immune dynamics

Perspective

- Model use to explore the innate response & test control measures
- Model extension to represent the infection dynamic for whole pig